TGF-α POLYPEPTIDES, FUNCTIONAL FRAGMENTS AND METHODS OF USE THEREFOR

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. Application Serial No. 09/641,587, filed August 17, 2000, now abandoned which is a continuation-in-part of U.S. Application Serial No. 09/492,935, filed January 27, 2000, which is a continuation-in-part of 09/378,567, filed August 19, 1999, now abandoned all of which are herein incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates generally the field of tissue repair and more specifically to the use of transforming growth factor alpha (TGF-α) polypeptide, fragments and mimetics for stimulating stem cells proliferation, migration and differentiation.

BACKGROUND

[0003] Stem cells and tissue precursor cells play important roles in the development, regeneration and repair of organisms and particularly tissue and organs. Stimulation of tissue regeneration and repair can provide needed benefit to organisms suffering from injury, disorders or diseases which impair physiological functions increasing mortality and morbidity. For example, there are several disease treatments that could significantly benefit by having cells regenerate after injury or lesion formation. For example, in some instances, a particular treatment for a disease often detrimentally affects the subject being treated. One such example, is the administration of chemotherapeutic agents to subjects, which results in destruction of healthy cells, for example, cells of the gastrointestinal tract. Such chemotherapeutic agents include carmustine (BCNU), chlorambucil (Leukeran), cisplatin (Platinol), Cytarabine, doxorubicin (Adriamycin), fluorouracil (5-FU), methoxetrate (Mexate), taxol, CPT111, etoposide, and plicamycin (Mithracin) which are known for their

the large intestine showed an increase in T cell progenitor cells. Histological staining showed increased T cell progenitors as compared with untreated mice and appeared as new germinal foci. Such T cell progenitors positioned in the gastrointestinal tract represent a reservoir for CD4 helper cells needed against mucosal directed vaccine production mediated by priming with exogenous antigen. The T cell progenitor cells appear to be double null and thus naive. Accordingly, the T cell progenitor cell response to TGF-α and TGF-α mimetics provides the utility for such compounds to provide a strong mucosal immunity response and usefulness as a mucosal vaccine and as a universal stem cell adjuvant.

[0072] During a course of therapy organs may be targeted by specific chemical agents, however, organ damage can be a side effect. In United States patent application 09/299,473 filed 26 April 1999 (the disclosure of which is incorporated by reference herein), now abandoned the effects of increasing hematopoiesis based upon hematopoietic injury from cytotoxic cancer therapy is described. These data can be further expanded to organ damage caused by chemicals known to cause specific organ damage. As shown below, gentamycin is an antibiotic known to cause kidney damage as a dose-limiting side effect. Histological data shows that the kidney damage seen in glomeruli of kidneys is alleviated by concurrent and subsequent administration of a TGF-α polypeptide (in this case a TGF-α57 polypeptide was used). Kidney damage can also occur following exposure to cancer chemotherapeutic agent, such as cis platinum, or gentamycin or the toxin from *E. coli* 0H1:37 from undercooked contaminated meats. Intestinal damage can occur form many cancer chemotherapeutic agents, cholera toxin, and the like. Lungs can be damaged by the anti-cancer agent bleomycin. Accordingly, administration of a TGF-α polypeptide, fragments, or mimetic before, during and following exposure to an organ toxic agent can prevent organ damage.

[0073] In addition, administration of a TGF-α polypeptide, fragments, and mimetic to regenerate damaged tissue, for example, in kidney, an organ sensitive to such damage, is also disclosed herein. In an *in vivo* experiment, mice were administered 10 mg/kg of Cis-platinum as a single ip injection and treated mice administered 10 μg/kg a human TGF-α57 (R&D Systems, Minneapolis, MN). TGF-α57 was administered just before CP and in two additional doses after, by ip administration for a general systemic effect. Several organs or